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Please find below and/or attached an Office communication concerning this application or proceeding.

24-

Office Action Summary	Application No. 09/910,469	Applicant(s) SCHWEITZER ET AL.	
	Examiner BJ Forman	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-308 and 315-372 is/are pending in the application.
- 4a) Of the above claim(s) 1-274 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 275-308 and 315-375 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1634

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 21 January 2004 in which the specification was amended, claims 275-281, 283-286, 291-308 315-326 were amended, claims 309-314 were canceled and claims 327-372 were added. And further in response to Supplemental Disclosure Statements and references submitted 21 January 2004 and 6 April 14, 2004. All of the amendments have been thoroughly reviewed and entered. The previous objections and rejections in the Office Action dated 21 August 2003, not reiterated below, are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed and are discussed below. New grounds for rejection necessitated by amendment and/or Supplemental Information Disclosure Statements are discussed.

Claims 1-274 are withdrawn. Applicant is reminded that the text of withdrawn claims does not need to be reiterated in the "Listing of Claims" section of the Response.

Claims 275-308 and 315-372 are under prosecution.

Information Disclosure Statement

2. Supplemental Disclosures statements of 21 January 2004 and 6 April 14, 2004 are acknowledged. The references listed on the 1449s have been considered unless lined-through. References for which only the Abstract was considered are so indicated. Non-English Language documents have not been considered and are noted as such on the 1449. The reference submitted 6 April 2004 was submitted in part. As noted on the 1449, pages 52-54 and 57 were submitted and considered. Pages 55 and 56 were not submitted. Page 57 ends in the middle of a sentence that indicates that the complete article contains at least a page 58.

Art Unit: 1634

Furthermore, the portion of the reference listing the references cited in the reference is missing.

The submitted portions of the reference have been considered.

The references submitted 21 January 2004, which are listed on the 1449s, filed 18 October 2001 and 16 April 2001 have been considered. Any references not received or considered are so noted on the 1449.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 275-287, 289-290, 292, 297-308, 319-321, 323-325, 327-339, 341-342, 349-360, 365-366, 369-371 are rejected under 35 U.S.C. 102(b) as being anticipated by Kool (U.S. Patent No. 6,077,668 issued 20 June 2000).

The claims are broadly drawn to methods of modifying a nucleic acid comprising the steps of contacting a conjugate comprising a nucleic acid and synthetic binding unit (e.g. nucleic acid analog) with an enzyme with reagents and under conditions for nucleic acid modification. The claimed conjugate encompasses a circular template comprising analogs, a primer comprising analogs, and a multimer comprising analogs all of which are taught by Kool

Art Unit: 1634

as discussed below. Because all of these conjugates are encompassed by the claims, various methods of modifying the conjugates are also encompassed by the claims.

Regarding Claim 275, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the synthetic binding unit is a pRNA (Column 13, line 56-Column 14, line 11). Kool specifically teaches their nucleotides Includes “naturally occurring **and**/or synthetic nucleotides, nucleotide analogs, and nucleotide derivatives” (Column 13, lines 57-60) e.g. pRNA (Column 13, line 56-Column 14, line 11).

Regarding Claim 276, Kool discloses method further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) wherein the reagents include a nucleic acid with hybridizes to the nucleic acid of the conjugate i.e. primer (Column 5, lines 34-53).

Regarding Claim 277, Kool discloses the method further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) wherein the other reagents includes modified (i.e. labeled) nucleoside triphosphates (Column 5, lines 34-53).

Regarding Claim 278, Kool discloses the method wherein the enzyme is selected from a polymerase (Column 5, lines 14-26), a ligase (Column 10, lines 9-64) and a restriction endonuclease (Example 3, Column 26, Scheme II).

Art Unit: 1634

Regarding Claim 279, Kool discloses the method wherein the enzyme is ligase and the conjugate is modified by ligation of a terminus of the nucleic acid to at least one additional nucleic acid e.g. linker (Column 10, line 27-Column 11, line 2).

Regarding Claim 280, Kool disclose the method wherein the ligation is template dependent and the nucleic acid of the conjugate and the additional nucleic acids are hybridized to adjacent sequences of a template i.e. splint (Example 26, Column 45).

Regarding Claim 281, Kool discloses the method wherein the ligation is template independent and the nucleic acid of the conjugate and the additional nucleic acids are single stranded (Column 10, line 27-Column 11, line 2).

Regarding Claim 282, Kool discloses the method wherein the ligase is T4 RNA ligase (Column 10, lines 62-65).

Regarding Claim 283, Kool discloses the method wherein the ligation is blunt-ended and the nucleic acid of the conjugate and the additional nucleic acids (i.e. adapter) are double stranded i.e. adapter is hybridized to the precircle thereby juxtaposing the 5' and 3' ends of the precircle which are then ligated (Column 10, lines 59-64 and Column 11, lines 3-24).

Regarding Claim 284, Kool discloses the method further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label, Column 5, lines 34-53) wherein the enzyme is a polymerase, wherein the nucleic acid of the conjugate has an unblocked 3' terminus, wherein the other reagents comprise a template to which the unblocked terminus hybridizes and wherein the nucleic acid is modified by the addition of at least one nucleoside complementary to the template at the 3' terminus i.e. in this embodiment, Kool teaches a biotinylated (analog) oligonucleotide as the conjugate having an unblocked 3' terminus which, when contacted with the circular template and a polymerase, is modified by addition of a nucleoside complementary to the template (Example 31, Column 51, line 61-Column 52, line 17).

Art Unit: 1634

Regarding Claim 285, Kool discloses the method of Claim 284 wherein the resulting modified conjugates are sequenced using dideoxynucleotides (Example 17, Column 39, lines 15-44).

Regarding Claim 286, Kool discloses the method of Claim 284 wherein a labeled nucleotide is added to the conjugate (Example 31, Column 52, lines 3-7).

Regarding Claim 287, Kool discloses the method of Claim 284 wherein the template is derived from a biological sample i.e. the circular template is derived from any organism (Column 10, lines 20-24).

Regarding Claim 289, Kool discloses the method of Claim 284 wherein the polymerase is selected from DNA polymerase, RNA polymerase and reverse transcriptase (Column 5, lines 14-33).

Regarding Claim 290, Kool discloses the method of Claim 284 wherein at least a portion of the template is amplified i.e. a multimer is produced comprising multiple copies of the circular template (Example 31, Column 51, line 61-Column 52, line 17).

Regarding Claim 292, Kool discloses the method of Claim 284 further comprising contacting the conjugate with a restriction endonuclease and wherein the conjugate comprises a recognition sequence 5' of the 3' terminus which hybridizes to the template and wherein at least a portion of the template is amplified by strand displacement (Column 8, lines 36-57 and Column 9, lines 56-Column 10, line 9 and Fig. 1).

Regarding Claim 297, Kool discloses the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is a restriction endonuclease and the other reagents comprise a target nucleic acid (i.e. short DNA strand) which hybridizes to the conjugate and wherein the conjugate and the target are cleaved by the restriction endonuclease (Column 21, lines 1-10).

Art Unit: 1634

Regarding Claim 298, Kool discloses the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is a restriction enzyme wherein the other reagents comprise a target nucleic acid to which the conjugate hybridizes and wherein the conjugate (i.e. multimer) is cleaved by the restriction enzyme but not the target (i.e. circular template) (Example 31, Column 51, line 61-Column 52, line 17 and Fig. 1).

Regarding Claim 299, Kool discloses the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is a restriction enzyme wherein the other reagents comprise a target nucleic acid to which the conjugate hybridizes and wherein the target (i.e. circular template) is cleaved by the restriction enzyme but conjugate (i.e. multimer) not the (Example 31, Column 51, line 61-Column 52, line 17 and Fig. 1). In this embodiment, the conjugate is the circular template comprising analogs and the target is the multimer product that is cleaved by the restriction enzyme. As stated above, the claims are broadly drawn to encompass numerous and various embodiments as disclosed by Kool.

Regarding Claim 300, Kool disclose the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is RNAase H wherein other reagents comprise an RNA target to which a portion of the conjugate hybridizes and wherein the conjugate is degraded (i.e. cleaved) by the RNAase H (Column 22, lines 39-45).

Regarding Claims 301-308, Kool discloses the method of Claim 275 wherein the point of activity of the enzyme is at the point of conjugation of the nucleic acid and the synthetic binding unit i.e. the analog-containing primer is contacted by the polymerase and therefore the point of activity for the primer (Column 8, lines 37-57; Column 11, line 51-Column 12, line 40; and Column 18, lines 48-62).

Art Unit: 1634

Regarding Claim 319, Kool discloses the method wherein the nucleic acid is selected from the group consisting of DNA, RNA and chemically modified nucleic acids (Column 8, lines 61-66).

Regarding Claim 320, Kool discloses the method wherein the nucleic acid is selected from the group consisting of phosphorothioate nucleic acids, phosphorodithioate nucleic acids, methylphosphonate nucleic acids, 2'-o-methyl RNA, and 2'-fluoro RNA (Column 13, line 57-Column 14, line 11).

Regarding Claim 321, Kool discloses the method wherein the nucleic acid is PNA (Column 13, lines 57-65).

Regarding Claim 323, Kool discloses the method wherein the conjugate further comprises at least one labeling moiety e.g. the primer as conjugate is labeled (Column 13, lines 26-36).

Regarding Claim 324, Kool discloses the method wherein label is selected from fluorescent moiety, visible dye moiety, radioactive moiety, chemiluminescent moiety, biotin moiety (Column 17, lines 36-59).

Regarding Claim 325, Kool discloses the method wherein the labeling moiety is a fluorescent dye selected from fluorescein dyes, rhodamine dyes, Texas red dyes, Oregon green (Column 17, lines 50-59).

Regarding Claim 327, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the synthetic binding unit is a pRNA (Column 13, line 56-Column 14, line 11) and wherein the nucleic acid and the synthetic

Art Unit: 1634

binding unit are joined at a single attachment point i.e. during synthesis (Column 8, lines 37-57; Column 11, line 51-Column 12, line 40; and Column 18, lines 48-62). Furthermore, Kool specifically teaches their nucleotides Includes “naturally occurring **and**/or synthetic nucleotides, nucleotide analogs, and nucleotide derivatives” e.g. pRNA (Column 13, lines 57-60).

Regarding Claim 328, Kool discloses method further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) wherein the reagents include a nucleic acid with hybridizes to the nucleic acid of the conjugate i.e. primer (Column 5, lines 34-53).

Regarding Claim 329, Kool discloses the method further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) wherein the other reagents includes modified (i.e. labeled) nucleoside triphosphates (Column 5, lines 34-53).

Regarding Claim 330, Kool discloses the method wherein the enzyme is selected from a polymerase (Column 5, lines 14-26), a ligase (Column 10, lines 9-64) and a restriction endonuclease (Example 3, Column 26, Scheme II).

Regarding Claim 331, Kool discloses the method wherein the enzyme is ligase and the conjugate is modified by ligation of a terminus of the nucleic acid to at least one additional nucleic acid e.g. linker (Column 10, line 27-Column 11, line 2).

Regarding Claim 332, Kool disclose the method wherein the ligation is template dependent and the nucleic acid of the conjugate and the additional nucleic acids are hybridized to adjacent sequences of a template i.e. splint (Example 26, Column 45).

Regarding Claim 333, Kool discloses the method wherein the ligation is template independent and the nucleic acid of the conjugate and the additional nucleic acids are single stranded (Column 10, line 27-Column 11, line 2).

Art Unit: 1634

Regarding Claim 334, Kool discloses the method wherein the ligase is T4 RNA ligase (Column 10, lines 62-65).

Regarding Claim 335, Kool discloses the method wherein the ligation is blunt-ended and the nucleic acid of the conjugate and the additional nucleic acids (i.e. adapter) are double stranded i.e. adapter is hybridized to the precircle thereby juxtaposing the 5' and 3' ends of the precircle which are then ligated (Column 10, lines 59-64 and Column 11, lines 3-24).

Regarding Claim 336, Kool discloses the method further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label, Column 5, lines 34-53) wherein the enzyme is a polymerase, wherein the nucleic acid of the conjugate has an unblocked 3' terminus, wherein the other reagents comprise a template to which the unblocked terminus hybridizes and wherein the nucleic acid is modified by the addition of at least one nucleoside complementary to the template at the 3' terminus i.e. in this embodiment, Kool teaches a biotinylated (analog) oligonucleotide as the conjugate having an unblocked 3' terminus which, when contacted with the circular template and a polymerase, is modified by addition of a nucleoside complementary to the template (Example 31, Column 51, line 61-Column 52, line 17).

Regarding Claim 337, Kool discloses the method of Claim 284 wherein the resulting modified conjugates are sequenced using dideoxynucleotides (Example 17, Column 39, lines 15-44).

Regarding Claim 338, Kool discloses the method of Claim 284 wherein a labeled nucleotide is added to the conjugate (Example 31, Column 52, lines 3-7).

Regarding Claim 339, Kool discloses the method of Claim 284 wherein the template is derived from a biological sample i.e. the circular template is derived from any organism (Column 10, lines 20-24).

Art Unit: 1634

Regarding Claim 341, Kool discloses the method of Claim 284 wherein the polymerase is selected from DNA polymerase, RNA polymerase and reverse transcriptase (Column 5, lines 14-33).

Regarding Claim 342, Kool discloses the method of Claim 284 wherein at least a portion of the template is amplified i.e. a multimer is produce comprising multiple copies of the circular template (Example 31, Column 51, line 61-Column 52, line 17).

Regarding Claim 344, Kool discloses the method of Claim 284 further comprising contacting the conjugate with a restriction endonuclease and wherein the conjugate comprises a recognition sequence 5' of the 3' terminus which hybridizes to the template and wherein at least a portion of the template is amplified by strand displacement (Column 8, lines 36-57 and Column 9, lines 56-Column 10, line 9 and Fig. 1).

Regarding Claim 349, Kool discloses the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is a restriction endonuclease and the other reagents comprise a target nucleic acid (i.e. short DNA strand) which hybridizes to the conjugate and wherein the conjugate and the target are cleaved by the restriction endonuclease (Column 21, lines 1-10).

Regarding Claim 350, Kool discloses the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is a restriction enzyme wherein the other reagents comprise a target nucleic acid to which the conjugate hybridizes and wherein the conjugate (i.e. multimer) is cleaved by the restriction enzyme but not the target (i.e. circular template) (Example 31, Column 51, line 61-Column 52, line 17 and Fig. 1).

Regarding Claim 351, Kool discloses the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is a restriction enzyme wherein the other reagents

Art Unit: 1634

comprise a target nucleic acid to which the conjugate hybridizes and wherein the target (i.e. circular template) is cleaved by the restriction enzyme but conjugate (i.e. multimer) not the (Example 31, Column 51, line 61-Column 52, line 17 and Fig. 1). In this embodiment, the conjugate is the circular template comprising analogs and the target is the multimer product that is cleaved by the restriction enzyme. As stated above, the claims are broadly drawn to encompass numerous and various embodiments as disclosed by Kool.

Regarding Claim 352, Kool disclose the method of Claim 275 further comprising contacting the conjugate and enzyme with other reagents (e.g. triphosphates, detectable label) (Column 5, lines 34-53) wherein the enzyme is RNAase H wherein other reagents comprise an RNA target to which a portion of the conjugate hybridizes and wherein the conjugate is degraded (i.e. cleaved) by the RNAase H (Column 22, lines 39-45).

Regarding Claims 353-360, Kool discloses the method of Claim 275 wherein the point of activity of the enzyme is at the point of conjugation of the nucleic acid and the synthetic binding unit i.e. the analog-containing primer is contacted by the polymerase and therefore the point of activity for the primer (Column 8, lines 37-57; Column 11, line 51-Column 12, line 40; and Column 18, lines 48-62).

Regarding Claim 365, Kool discloses the method wherein the nucleic acid is selected from the group consisting of DNA, RNA and chemically modified nucleic acids (Column 8, lines 61-66).

Regarding Claim 366, Kool discloses the method wherein the nucleic acid is selected from the group consisting of phosphorothioate nucleic acids, phosphorodithioate nucleic acids, methylphosphonate nucleic acids, 2'-o-methyl RNA, and 2'-fluoro RNA (Column 13, line 57-Column 14, line 11).

Regarding Claim 367, Kool discloses the method wherein the nucleic acid is PNA (Column 13, lines 57-65).

Art Unit: 1634

Regarding Claim 369, Kool discloses the method wherein the conjugate further comprises at least one labeling moiety e.g. the primer as conjugate is labeled (Column 13, lines 26-36).

Regarding Claim 370, Kool discloses the method wherein label is selected from fluorescent moiety, visible dye moiety, radioactive moiety, chemiluminescent moiety, biotin moiety (Column 17, lines 36-59).

Regarding Claim 371, Kool discloses the method wherein the labeling moiety is a fluorescent dye selected from fluorescein dyes, rhodamine dyes, Texas red dyes, Oregon green (Column 17, lines 50-59).

Response to Arguments

5. Applicant argues that Kool describes their templates in the alternative as comprising nucleotides **or** modified nucleotides and therefore do not contain both nucleotides and modified nucleotides as instantly claimed. The argument has been considered but is not found persuasive because, as cited above, Kool specifically teaches their nucleotides Includes “naturally occurring **and**/or synthetic nucleotides, nucleotide analogs, and nucleotide derivatives” (Column 13, lines 57-60) e.g. pRNA (Column 13, line 57-Column 14, line 11).

Applicant further argues that Kool requires a polymerase to perform their methods in contrast to the instantly claimed synthetic binding unit which cannot be synthesized, amplified, process, ligated, fragmented or hydrolyzed by enzymes which are known from nucleic acid technology, such as polymerases, ligases, nucleases, restriction enzymes, etc. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Art Unit: 1634

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 288, 291, 340 and 343 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Zhang et al (U.S. Patent No. 5,876,924, issued 2 March 1999).

Regarding Claim 288 and 340, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the template is derived from a biological sample i.e. the circular template is derived from any organism (Column 10, lines 20-24) but they do not specifically teach the claimed organisms and samples. However, Zhang et al teach a similar method for modifying a nucleic acid comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. bead modified probe, Column 7, lines 8-30) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 43, line 56-Column 44, line 40) wherein the sample is selected from the group consisting of human materials and viral cultures whereby clinically important samples

Art Unit: 1634

are sensitively detected rapidly (Column 3, lines 3-9). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the human and viral sample detection of Zhang et al to the organism detection of Kool based on the clinical importance of human and viral detection as taught by Zhang et al (Column 3, lines 3-9).

Regarding Claim 291 and 343, Kool teaches the method wherein the polymerase is a thermostable polymerase (Column 13, lines 22-24) but they do not specifically teach thermocycling conditions. However, Zhang et al teach the similar method wherein the template is amplified utilizing a thermostable polymerase and thermocycling conditions whereby sequence-specific amplification is performed (Column 14, lines 1-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the thermocycling conditions of Zhang et al to the amplification of Kool to thereby provide amplification temperatures specific for the sequence to be amplified for the expected benefit of optimizing conditions for sequence-specific amplification as taught by Zhang et al (Column 14, lines 1-67).

8. Claim 293 and 345 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Berninger et al (U.S. Patent No. 5,194,370 issued 16 March 1993).

Regarding Claim 293 and 345, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally

Art Unit: 1634

occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the polymerase is RNA polymerase and containing RNAase H activity (Column 22, lines 39-45) but does not teach the polymerase is in a mixture comprising reverse transcriptase. However, mixtures of RNA polymerase, reverse transcriptase and RNAase H were well known in the art at the time the claimed invention was made as taught by Berninger et al (Column 13, lines 55-67).

Furthermore they teach the mixture produces nucleic acids functionally identical to the starting nucleic acids (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the polymerase mixture of Berninger et al to the RNA synthesis of Kool for the expected benefit of obtaining RNA molecules functionally identical to the starting RNA molecules as taught by Berninger et al (Abstract).

9. Claim 294-296 and 346-348 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Nelson et al (Methods in Enzymology, 1979, 68: 41-50).

Regarding Claims 294-296 and 346-348, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme which utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time

Art Unit: 1634

sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the polymerase is RNA polymerase and containing RNAase H activity and a labeled nucleic acid is added to the conjugate (Column 22, lines 39-45) but they do not teach the enzyme is a terminal transferase wherein a homopolymeric tail is added to the conjugate. However, terminal transferase addition of homopolymeric tails was well known in the art at the time the claimed invention was made as taught by Nelson et al who teach that addition of homopolymeric tails using terminal transferase eliminates the need for restriction sites and results in successful infection (page 42, second full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the terminal transferase addition of homopolymeric tails as taught by Nelson et al to the nucleic acid addition of Kool. One of ordinary skill in the art would have been motivated to do so based on the advantages taught by Nelson et al i.e. eliminates the need for restriction sites and results in successful infection (page 42, second full paragraph).

10. Claims 322, 326, 368 and 372 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Lannigan et al (U.S. Patent No. 6,399,302, filed 20 August 1999).

Regarding Claims 322, 326, 368 and 372, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes

Art Unit: 1634

naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the polymerase is RNA polymerase and containing RNAase H activity and a labeled nucleic acid is added to the conjugate (Column 22, lines 39-45) but they do not teach the nucleic acid is an aptamer wherein the conjugate is labeled with a quencher moiety. However, quencher labeled aptamers were well known in the art at the time the claimed invention was made as taught by Lannigan et al. who further teach that aptamers have the ability to form an array of shapes, sizes and configurations and therefore are capable of forming specific binding pairs with almost any compound (Column 1, lines 49-63). They further teach that the quencher labeled aptamers permits real-time detection of binding events (Column 10, lines 57-61). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the quencher-labeled nucleic acid aptamers of Lannigan et al to the nucleic acids of Kool to thereby provide nucleic acids which would form binding partner with virtually any compound wherein the binding event would be detected over time as taught by Lannigan et al (Column 1, lines 49-63 and Column 10, lines 57-61) for the expected benefit of detecting a binding partner for any compound for which a binding partner is desired (Column 1, lines 49-63).

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Art Unit: 1634

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

12. Claims 315-318 and 361-364 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1634

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to be 'BJ Forman', with a long, sweeping horizontal stroke extending to the right.

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
April 14, 2004